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Microcephaly, Muscular Build, Rhizomelia, and Cataracts: Description of a Possible Recessive Syndrome and Some Comments on the Use of Electronic Databases in Syndromology

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We report on a 7-year-old boy born of consanguineous parents with severe microcephaly (−5 SD) but borderline intelligence, juvenile cataract, muscular build, rhizomelic shortness of limbs predominantly of femora, advanced bone age, and micropenis. This combination of signs appears unique and may represent an undescribed, possibly autosomal recessive MCA syndrome. The use of LDDB and POSSUM in the workup of such "new syndromes" is reviewed. Three search strategies are discussed: single rare sign browsing, best combinatory fit using an array of key words, and combined rare signs scan. Pitfalls in the use of such databases and the some problems raised by inconsistent/incomplete encoding in those two popular, highly useful syndromology retrieval systems are discussed. Am. J. Med. Genet. 68:455–460, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: microcephaly; cataracts; muscular hypertrophy; rhizomelia; London dysmorphology database; POSSUM database

CLINICAL REPORT

Our propositus was the fourth child of first-cousin Turkish parents. Family history was not contributive. Father was 163 cm tall, with an OFC of 58.5 cm; the mother was 157 cm tall and had an OFC of 54 cm. The two elder brothers and the elder sister were phenotypically normal.

This boy was born at the 36th week of pregnancy. BW was 1,450 g, BL 38 cm, and OFC 27.6 cm (all << p3). He developed neonatal hepatitis and recovered spontaneously in 2 months. Investigations failed to discover a viral or metabolic cause. We saw him first at 3 months. Striking anomalies noted at this time included his appearance (Fig. 1) with sparse hair and brows, hypotelorism and micrognathia, short, bowed legs, and high arched palate. He was subsequently lost to follow-up. At age 6, a decrease in visual acuity was noted. Ophthalmologic investigation showed cataracts: a posterior polar cataract O.S. (visual acuity 6/10) and a posterior capsular cataract O.R. that was removed (pre-operative VA < 1/10).

When re-evaluated at age 8½, he was 120 cm tall. U/L ratio was 1.23 and arm span was 119 cm. He weighed 33 kg and had an OFC of 45 cm (−5 SD). His face had a square shape. There was hypotelorism (inner intercanthal distance 19 mm; outer intercanthal distance 80 mm), squint, a long nose, flat malar area, somewhat tented upper lip, high vaulted palate, crowded teeth, and micrognathia. Ears and hair were normal. He had a *hypertrophic muscular build* (not explained by physical activity), most striking in the thighs and shoulders (Fig. 2a,b), sloping shoulders, widely spaced nipples with moderate sternal depression, micropenis, hypoplastic scrotum, and rhizomelic shortness of upper and lower limbs, with limitation of extension of elbows. Hands and feet appeared disproportionately large (hand 17 cm, palm 10.5 cm, foot 23 cm), with wide halluces and toe 2–3 cutaneous syndactyly (Fig. 2c). There was no evidence of puberty. Neurological status was normal.

An MRI showed a small but otherwise normal brain. EEG, electromyography, and conduction velocities were normal. CK levels were not increased. Skeletal survey was considered normal, except for short but normally modelled femoral and humeral diaphyses, thick femoral necks with coxa valga, and advanced wrist bone maturation (11.5 years). Endocrine investigations showed normal prepubertal values for testosterone,

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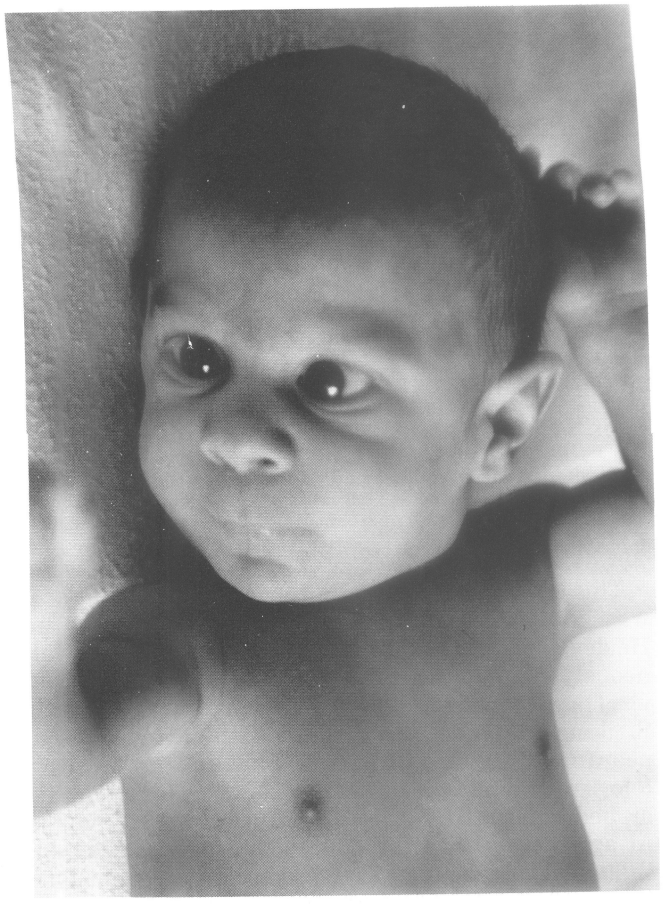


Fig. 1. Propositus aged 3 months; note hypotelorism.

DHEA sulphate, delta-4-androstenedione, cortisol, 11-deoxycortisol and 17-OH-progesterone, and normal hGH and somatomedin C levels. Karyotype and FRAXA expansion were normal. Blood and urinary metabolic screenings were normal for aminoacids, organic acids, oligosaccharides, uridyl-galactose transferase, carnitine and acylcarnitines, VLCFA and 7-OH-cholesterol. IQ was rated 65 (WISC). He was very friendly.

DISCUSSION

The delineation of a "new" syndrome is based on the subjective appraisal that a particular combination of individually nonspecific anomalies represents a specific entity. The child reported here, born of consanguineous parents, has a syndrome of severe microcephaly (with mild retardation), muscular build, micropenis, cataracts, and rhizomelia with advanced bone age. Table I summarises the number of syndromes coded with each finding, in the third version of the London Dysmorphology Database [Winter and Baraitser, 1995] and the fourth version of POSSUM [Bankier et al., 1995]. It shows how nonspecific these signs are, taken one by one, the most selective traits (and thus the most interesting approach to a delineation of this syndrome) being the advanced bone age and muscular build.

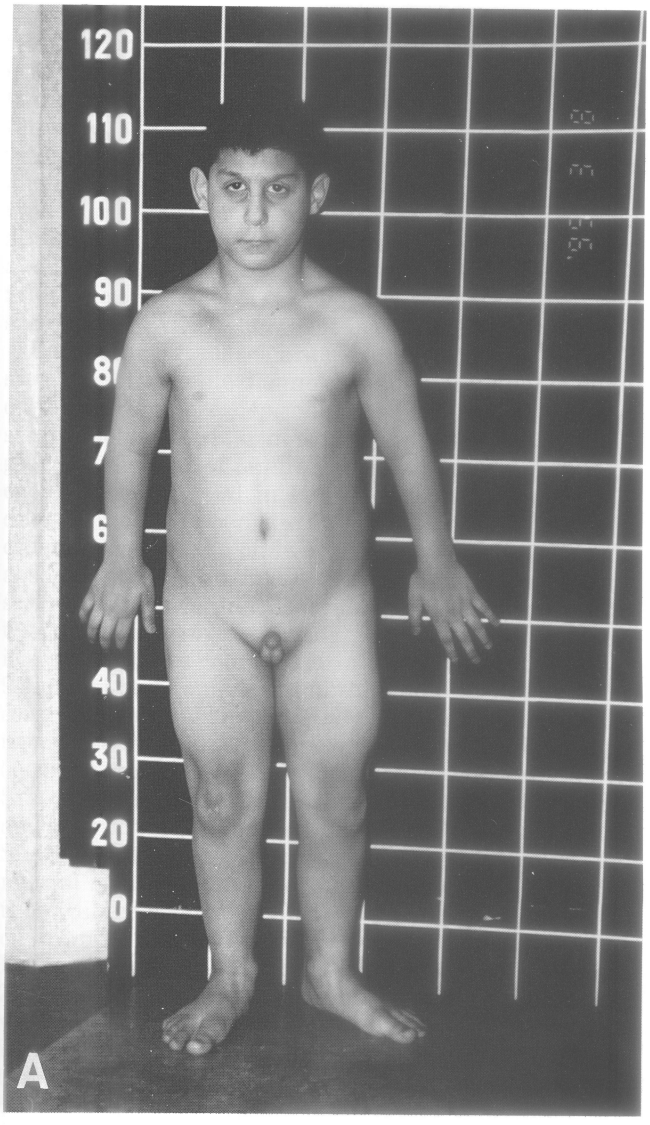
TABLE I. Number of Syndromes Retrieved in LDDB and POSSUM for 9 Keyword Signs in Our Propositus

		POSSUM	
Sign	LDDB	Full set	Excluding chromosomes
Microcephaly	415	486	377
Muscular build	11	21	21
Cataract	237	200	177
Rhizomelia (upper limb)	65	73[a]	71[a]
Rhizomelia (lower limb)	50		
Advanced bone age	49	41	37
Micrognathia	434	553	438
Small penis	148	228	164
Mental retardation	990	1,008	852

[a] POSSUM does not distinguish upper limb rhizomelia from lower limb rhizomelia.

A first approach to the use of electronic databases is to browse syndromes sharing one of those rare traits. Advanced bone age is observed in several overgrowth syndromes, such as Weaver syndrome, all easily discarded in this small-for-date child. Other aetiologies of advanced bone age, such as Desbuquois "chondrodystrophy," endocrine disturbances of GH or androgen hypersecretion, were ruled out. Muscular build is sometimes observed in hypothyroidism (Kocher-Debré-Sémelaigne syndrome), in most forms of lipodystrophy with insulin resistance, and in rare MCA syndromes, as Myhre [Garcia-Cruz et al., 1993; Myhre et al., 1981] and GOMBO syndromes [Verloes et al., 1989], which could be related entities [Bottani and Verloes, 1995]. None of those diagnoses fits the MCA pattern observed here.

A second, opposite way to use databases in differential diagnosis is to browse known syndromes for any combination of key features, using if possible rare traits and avoiding redundancy (this is easier to manage in LDDB, as several related items may be combined in a single line). We performed such a query in LDDB and POSSUM using 8 (POSSUM) or 9 (LDDB) signs. Results are tabulated comparatively (Table II), keeping only those with at least 5 "hits" in both systems (plus those with 4 hits including rhizomelia, in POSSUM, to compensate for the presence of two key words for rhizomelia in LDDB). Seven or 8 syndromes (depending on the splitting of Kivlin syndrome) are found with both systems, 6 further syndromes give at least 4 "hits" with POSSUM, whereas 3 others are selected in LDDB. The highest score is 5/8. None of those diagnoses could be retained. The less discordant one was Martsolf syndrome [Hennekam et al., 1988; Martsolf et al., 1978], a combination of severe mental retardation, cataracts, primary hypogonadism, and short stature. Although it was not selected by our retrieval systems, Mirhoseini-Holmes-Watson syndrome, which combines mental retardation, variable short stature, cataracts, microbrachycephaly, ataxia, and hypergonadotropic hypogonadism [Mendez et al., 1985; Mirhosseini et al., 1972] was also considered, but retinal degeneration, which is a prominent component of that syndrome, was not observed in our propositus.



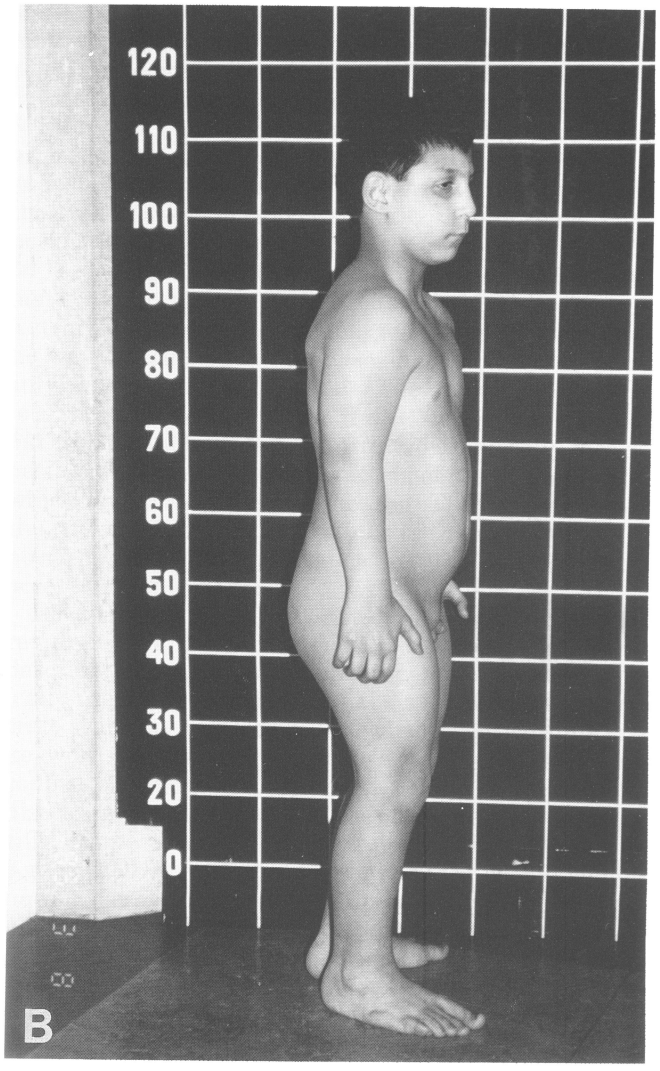


Fig. 2. Propositus aged 7. **A**. Frontal view: note muscular hypertrophy of limb girdles, short femora and micropenis. **B**. Profile: large hands and feet, and micrognathia. **C**. Large, short halluces and toes 2–3 syndactyly.

TABLE II. Comparison of LDDB v3 (L) and POSSUM v4 (P)*

Syndrome denomination	Base	Microcephaly	Muscular build	Cataract	Rhizomelia[a]	Advanced bone age	Micrognathia	Mental retardation	Small penis	Score
1. Desbuquois chondro-	L	X	-	-	UL LL	X	X	X	-	6
dysplasia	P	X	-	-	X	X	X	X	-	5
2. Martsolf syndrome	L	X	-	X	-	-	X	X	X	5
	P	X	-	X	-	-	-	X	X	4
3. Rhizomelic chondro-	L	X	-	X	UL LL	-	-	X	-	5
dysplasia punctata	P	X	-	X	X	-	-	X	-	4
4. Hallermann-Streiff-	L	-	-	X	-	-	X	X	X	4
François syndrome	P	X	-	X	-	-	X	X	X	5
5. Kivlin syndrome	L	-	-	X	UL LL	-	X	X	-	5
(Peter's plus syndrome)	P	X	-	X	X	-	X	X	-	5
5'. Sclerocomea, short stature[b]	P	X	-	-	X	-	X	X	-	4
6. Urbach rhizomelic	L	X	-	-	UL	-	X	X	-	4
skeletal dysplasia	P	X	-	-	X	-	X	X	-	4
7. Smith-Lemli-Opitz	L	X	-	X	-	-	X	X	-	4
syndrome (mild)	P	X	-	X	-	-	X	X	X	5
8. Smith-Lemli-Opitz	L	-	-	X	-	-	X	-	-	2
syndrome (severe)	P	X	-	X	-	-	X	X	X	5
9. Beckwith-	L	X	X	-	-	X	-	X	X	5
Wiedemann syndrome	P	X	X	-	-	X	-	X	X	5
10. Robin sequence,	L	-	-	-	UL LL	-	X	X	-	4
mesomelia, poly-	P	X	-	-	X	-	X	X	-	4
dactyly										
11. Cerebro-oculo-	L	-	-	X	-	-	X	X	-	3
muscular syndrome	P	X	-	X	-	-	X	X	X	5
12. Ceballos-Quintal	L	X	-	X	UL	-	-	-	-	3
Tar-like syndrome	P	X	-	X	X	-	-	X	-	4
13. Microcephalic osteo-	L		-	-	-	-	X	X	-	3
dysplastic dwarfism 1	P		-	-	X	-	X	X	-	4
14. Mulvihill-Smith	L	X	-	-	-	-	X	X	-	3
syndrome	P	X	-	-	-	X	X	X	X	5
15. Stickler syndrome	L	X	-	X	UL LL	-	X	X	-	6
	P	-	-	X	-	-	X	-	-	2
16. Warfarin embryop-	L	X	-	X	UL LL	-	-	X	-	5
athy	P	X	-	-	-	-	-	X	-	2
17. Stanescu dominant	L	X	-	-	UL	-	X		-	3
osteosclerosis	P	X	X	-	X	-	X	-	-	4

* All syndromes with at least 5 matches in one system are listed, and those with 4 matches in POSSUM, one of them being rhizomelia (as rhizomelia, may count twice in LDDB). The table is divided into 3 sections: syndromes retrieved in both LDDB and POSSUM, syndromes retrieved by POSSUM alone, and syndromes retrieved by LDDB alone. Xs represent positive signs. The score indicated the number of matched.

[a] Rhizomelia is a single keyword in POSSUM, but is divided in upper (UL) and lower limb (LL) rhizomelia in LDDB.

[b] Part of Kivlin syndrome in LDDB.

A third strategy is to pick out two or three rare key features and to do a search on these. This requires several trials and even more syndromologic skills than the two previous approaches. Depending on the "feeling" of the case, we could have selected other combinations, which would have yielded other differential diagnoses, for instance a combination of advanced bone age and muscular hypertrophy, or a combination of cataracts and 2–3 syndactyly, or a combination of hypotelorism and 2–3 syndactyly (but these would not have been useful in the discussion, as 2–3 syndactyly is not a specific sign in POSSUM, whereas it is in LDDB).

Electronic databases are a fantastic means for rapid scanning of possible diagnoses and an invaluable method for retrieving exceptional case reports. No modern syndromologist could do without them, and the still growing number of published phenotypes makes them even more essential in clinical practice. The level of concordance between the two systems is rather good, considering the use of different key word lists and the absence of an universally accepted language for describing dysmorphic features. Among 17 disorders retrieved here (and considering "rhizomelia" as one manifestation), 3 are concordant in the encoding of our 8 or 9 signs, 9 have one discordance, and 5 have 2 or 3 discordant features. The most surprising discrepancies between the two systems concern Warfarin embryopathy (cataract and rhizomelia mentioned only in LDDB), Stickler syndrome (mental retardation, rhizomelia, and microcephaly encoded only in LDDB), and severe Smith-Lemli-Opitz (microcephaly, small penis, and mental retardation quoted only in POSSUM). Some of those discrepancies result from the opinion of authors on lumping and splitting of some ill-delimited entities. For instance, rhizomelia is a feature of Weissenbacher-Zweymüller syndrome, but not of typical adult patients with Stickler syndrome. Depending on whether it is or is not included in the frame of the Stickler syndrome (see its entry in LDDB for a discussion), rhizomelia will or will not be among the descriptors of Stickler syndrome. A further unresolved problem is the incorporation of rare/coincidental features in the trait list of a given syndrome. Mental retardation has been reported only in one family with Stickler syndrome. Depending on the importance set to this point by the authors (or on their general philosophy about syndromologic databases), we may understand that the feature is retained by LDDB, but neglected by POSSUM. This difficulty could be alleviated by implementing some form of facultative weighing system for the key words. The simplest would be a dichotomic definition of "minimal/major" versus "minor/secondary" criteria. A most sophisticated system could associate each sign with some quantitative expression of the frequency of the trait. Even if a weighting system appears a desirable enhancement of the softwares, those policies would unfortunately not completely solve the problems, as we do not know in most syndromes how closely the published cases reflect the "true" spectrum of the disease. In both softwares, another weak point, in this context, is the impossibility to retrieve directly the article in which a trait has been described. This is somewhat less problematic in LDDB, in which a wider bibliography is given (we may reasonably hope that all papers used for the list of signs are quoted), than in POSSUM, which has drastically self-restricted its bibliographic references.

From this small test (which should not be considered as a comparative performance test, but rather as a snapshot view of some difficulties inherent in the use of those databases), it appears that both syndrome diagnosis and differential diagnosis should not rely entirely on the available databases (in their current state), as non-coherent encoding still exists. Of course, looking at a straight match of the number of features is a simplistic way of using such databases and certainly not the only way to a proper diagnosis. The overall appearance is another important part of the Gestalt of a syndrome, but this visual approach is intuitive and totally incompatible with the analytic dissection of the phenotype on which retrieval systems are based. The comparison of the patient with the illustrations of the retrieved diagnoses is of major importance in the final rejection/acceptance of a diagnosis.

Electronic databases do not do diagnosis. They still require the skill of the dysmorphologist to evaluate and describe the patients appropriately and to analyse critically the diagnoses raised by the systems. Both single trait scanning and combinatory search with multiple keywords are necessary. Because of still perfectible encoding, one must assume that a combination of 2 or 3 discriminating signs (or the use of "mandatory" or "specific" toggles) may eventually miss a correct diagnosis, e.g., in LDDB, you would not get SLO2 with a combination, set as mandatory, of microcephaly and micropenis (which, of course, is less common than ambiguous genitalia, but still possible). It should be a general duty for clinical geneticists to provide feedback to the authors with remarks and errors.

More than ever, electronic syndromology databases should be considered as "systems for experts" and not expert systems (R. Winter).

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